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A. D. BLOSE

Technical Information Officer

RESPONSE OF THE CARDIOVASCULAR  
SYSTEM TO VIBRATION AND COMBINED STRESSES

Progress Report  
September 1, 1975 - September 30, 1976  
Air Force Office of Scientific Research  
Contract No. F44260-74-C-0012  
University of Kentucky

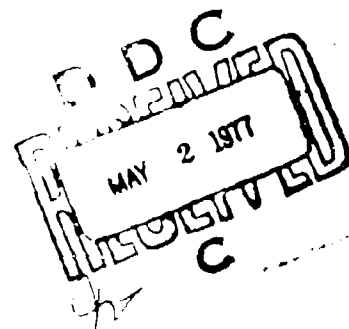
Principal Investigator: Charles F. Knapp, Ph.D.

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Lexington, Kentucky 40506

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## SUMMARY

Low frequency, sinusoidal accelerations are being used to quantify the frequency response of cardiovascular regulation in awake, chronically instrumented canines. Current emphasis is being placed on the use of pharmacologic blocking agents to delineate the relative contributions of cardiac and peripheral vascular mechanisms required to maintain circulatory integrity during time-dependent acceleration loadings. The accelerations are produced by a specially modified, 50 foot diameter, centrifuge. With the aid of a slowly rotating platform, the system is capable of producing  $\pm 3 g_z$  sinusoidal acceleration at frequencies from 0.001 to 1.8 Hz.

Chronically instrumented canines (initially tranquilized with Innovar) are restrained horizontally in a couch mounted to the centrifuge platform. The measured variables include heart rate, ECG, aortic flow and pressure, right and left ventricular pressures, coronary flow and centrifuge acceleration. The initial test series consists of a  $+2 g_z$  and a  $-2 g_z$  step input acceleration (1 to 2 g's per sec) followed by  $\pm 2 g_z$  sinusoidal accelerations from 0.005 to 1.8 Hz. Individual and combinations of pharmacologic blockers (Phentolamine, Atropine, and Propranolol) are then administered to each animal, producing an experimental state from which a particular neural control pathway has been removed. Fourteen experiments using 8 unblocked dogs and 2 experiments using 2 dogs in the unblocked and blocked states have been conducted to date.

For both the  $+2 g_z$  and  $-2 g_z$  step inputs, the initial (2-5 sec) responses were often similar, consisting of an increase in heart rate and cardiac output, with a drop in apparent vascular impedance; although for the  $+2 g_z$  (blood to the feet) case there was a hydrostatic drop in pressure, with the opposite being true for the  $-2 g_z$  case (blood to the head). Following this initial response, the  $+2 g_z$  tests consistently evoked a sympathetic response

(further increase in heart rate accompanied by an increase in max dp/dt and impedance) resulting in a recovery of aortic pressure within 15 to 20 seconds. In contrast, the  $-2 g_z$  steady state with its elevated aortic and left and right ventricular diastolic pressures is characterized by a pronounced rhythm in heart rate, and all pressure and flow variables. This rhythm appears to be under parasympathetic control, and is established both in magnitude and periodicity within 10 seconds of the input stress.

In almost every case, the frequency of the cyclic heart rate changes observed in the unblocked animals was the same as that of the sinusoidal acceleration for frequencies up to 0.3 Hz. The peak to peak amplitude of the heart rate oscillations increased with increasing frequency between 0.005 and 0.1 Hz, reaching a maximum (average change of 127 bpm) in the range of .02 to 0.1 Hz, and then decreased rapidly, with minimal oscillations observed after 0.3 Hz. Peak to peak oscillations in aortic pressure were similar to those observed for the heart rate, with maximal oscillations in the 0.03 to 0.06 Hz range. Preliminary results using pharmacologic blockade (heart rate constant and periphery blocked, 'hydraulic dog') indicate that the open loop response of aortic pressure is maximal between 0.04 and 0.06 Hz. A comparison of the unblocked and totally blocked responses indicates that peripheral mechanisms are operative up to about 0.03 Hz.

## INTRODUCTION

Our long range research program is designed to investigate the response of the cardiovascular system to whole body, time varying acceleration over a wide frequency range. This program can be placed in perspective by examining the data base which is currently being developed by that section of the research community concerned with acceleration and vibration stress (Figure 1). A considerable amount of data has been generated by our group and others which quantifies vibration-induced cardiovascular responses in the 2-12Hz frequency range. A summary of these studies has been reported in previous progress reports. To date, the studies at the low end of the vibration range have been dictated by the limitations of conventional vibration platforms, which require excessive strokes in order to achieve reasonable g levels at low frequencies. At the limit of the low end of the spectrum, considerable amounts of data are being collected by those groups investigating cardiovascular responses to sustained acceleration loadings (Figure 1). It has become apparent that as the data base developed over the years, studies were conducted as if sustained acceleration and whole body vibration, greater than 1.5 Hz, were two unrelated phenomena. This unfortunate delineation of the two extremes of acceleration essentially set boundaries producing an interim region between sustained acceleration and acceleration less than 1.5 Hz which contains very limited information; information essential to assess the potential hazards to personnel flying high performance aircraft capable of producing acceleration profiles which tax cardiovascular control.

This progress report describes our efforts to systematically investigate the response of the cardiovascular system of intact canines to time-varying acceleration from 0.001 to 1.5 Hz. The investigation is designed to 1) quantify the responses of the cardiovascular system to these low frequency accel-



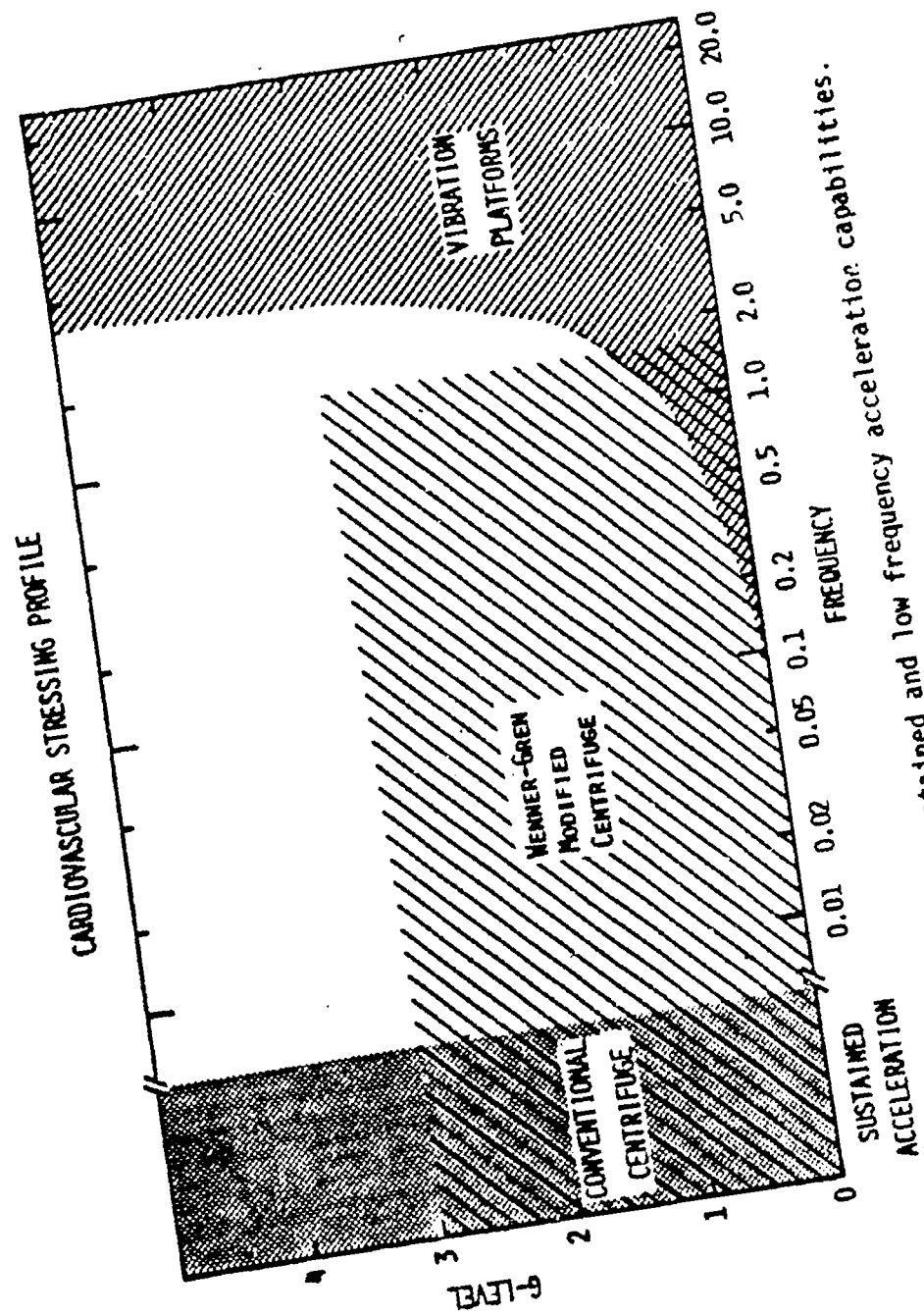


Fig. 1. Wenner-Gren sustained and low frequency acceleration capabilities.

eration loadings and 2) to delineate the relative contribution of cardiac and peripheral vascular mechanisms enacted to minimize the circulatory disturbance produced by the acceleration loadings.

The rationale for these studies is based on the premise that the design of effective countermeasures to acceleration stress depends upon the understanding of the mechanisms responsible for cardiovascular regulation. Studies reported in this document were performed using chronically instrumented canines because of the invasive nature of the instrumentation required for assessing cardiovascular responses. The forcing function to the cardiovascular system consisted of step input (sustained) accelerations and sinusoidally-varying accelerations from 0.001 to 1.5Hz. This approach has several important aspects in addition to merely quantifying cardiovascular responses to acceleration loadings. 1) Both step input and sinusoidally-varying acceleration profiles are used in classical approaches to quantifying the frequency response of any feedback control system. 2) The acceleration forcing function is a very realistic stress loading which approximates stresses encountered by personnel flying high speed terrain-following aircraft. 3) An advantage of using time-dependent acceleration as a means to provide a pressure disturbance in the cardiovascular system is its noninvasive nature when compared to those disturbances associated with classical studies of cardiovascular regulation.<sup>1-6</sup> 4) Because of the nature of whole body acceleration, both pressure and volume disturbances are produced throughout the cardiovascular system. This makes the input global and somewhat more complicated than the conventional techniques using local pressure disturbances such as periodic occlusions of the aorta<sup>2</sup> or sinusoidal pressure variations at the isolated carotid sinus.<sup>4,5</sup> Because of the global aspects of the disturbances, the techniques employed to isolate the various feedback pathways must also be global in nature. Such requirements necessitate the use of pharmacologic blocking agents.

Thus, the use of pharmacologic blocking agents was initiated in the second phase of this study to delineate the relative contribution of cardiac and peripheral vascular mechanisms; two mechanisms believed to be the principal modes of adjustment required to maintain circulatory integrity during acceleration loading.<sup>1-2</sup> Administration of pharmacologic blocking agents has several advantages over other approaches in that 1) it is a standard procedure with many of its limitations well documented; 2) the effect of these agents is distributed throughout the system and does not have the uncertainty associated with attempts at total denervation; and 3) the use of these agents allows for repeated blocked-non-blocked studies on the same animal without compromising the integrity of the preparation.

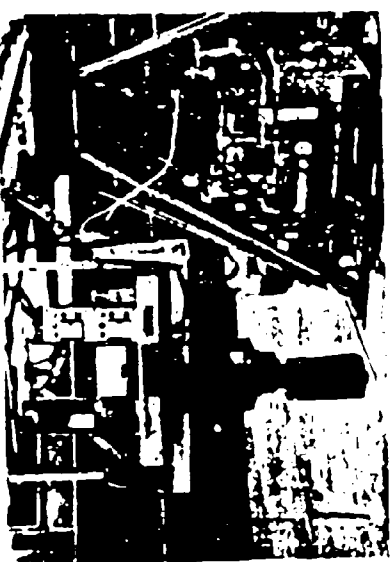
Thus, the approach used in this study is considered to be realistic from the standpoint of the input function, and sound from the standpoint of evaluating the frequency response of cardiovascular regulation. It is believed that the studies reported below in combination with the continuing blocker studies scheduled for the coming year will provide understanding of the relative contribution of the mechanisms responsible for cardiovascular regulation during acceleration stress. The ultimate aim of this basic research effort is to provide the background required for the design and implementation of human investigations which will lead to improved protective equipment and operational procedures for military personnel exposed to the acceleration environment resulting from the optimal utilization of advanced aerospace systems.

## METHODS

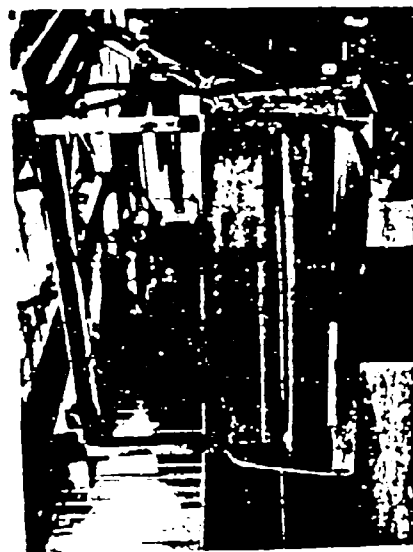
The low frequency acceleration loadings were produced by the modified 50 foot diameter centrifuge shown in Figure 2. This system is capable of producing  $\pm g_z$  sinusoidal accelerations up to 1.8Hz, at g levels up to  $\pm 3g_z$ . Mounted to the large arm of the centrifuge is a platform capable of rotation speeds from 0.05 to 110 rpm. With the large centrifuge arm rotating at an appropriate rpm to produce the desired radial peak acceleration, an initiation of the platform rotation will produce sinusoidal  $g_z$  acceleration loadings. This configuration will also produce a  $g_y$  acceleration  $90^\circ$  out of phase of that for  $g_z$ . While cardiovascular responses to  $g_y$  sustained acceleration have been shown to be relatively small when compared to those of the  $g_z$  direction (current study), their potential influence cannot be totally disregarded when interpreting the data from these experiments.

It may also be pointed out that step changes in  $g_z$  acceleration can be produced by beginning the test with the animal's  $g_z$  axis perpendicular to the large axis of the centrifuge until the desired rpm of the large arm has been reached. At this time a  $90^\circ$  rotation can produce a + or - sustained  $g_z$  loading of the cardiovascular system within one second (rates up 3 g/sec are possible). Step inputs of this type to the system also can be used to quantify the frequency response of cardiovascular regulation.

Chronically instrumented canines (weighing from 18 to 22 Kg) were used in this study. A detailed explanation of this animal preparation can be found in previous progress reports. Briefly, the animals were implanted with an electromagnetic flow probe (Zepeda) around the ascending aorta, a pressure gauge (Königsberg) in the apex of the left ventricle, often an electromagnetic flow probe (Biotronex) on the left circumflex coronary artery, and a



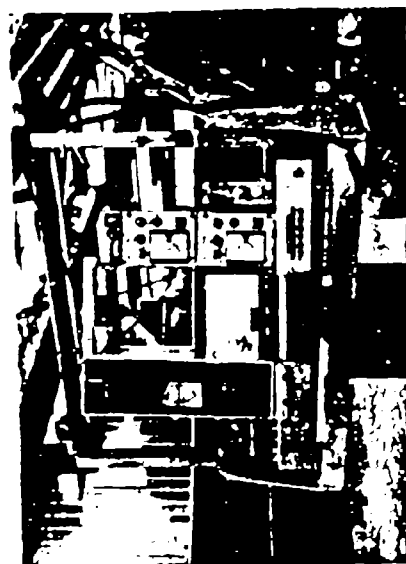
b



d



a



c

Figure 2. Successive close-ups of Wenner-Gren's centrifuge modification:  
 a. Rotating platform mounted on arm of conventional centrifuge  
 b. Close-up of modification detailing rotating platform with associated drive train  
 c. Close-up of modification detailing animal restraint with associated instrumentation  
 d. Time exposure of rotating platform

cannula in the right atrium for the administration of drugs. On the day of the experiment the animals were lightly tranquilized with Innovar. A Millar pressure gauge was placed in the left ventricle via the femoral artery to calibrate the Konigsberg pressure gauge and then pulled back and positioned in the aorta for measuring aortic pressure. A second Millar was positioned via the femoral vein, in the right ventricle. The animals were then restrained horizontally in the couch mounted to the centrifuge platform. The measured variables included: heart rate, ECG, aortic flow and pressure, right and left ventricular pressure, coronary flow and centrifuge acceleration. The initial test series consisted of a  $+2g_y$ ,  $+2g_z$ ,  $-2g_y$  and a  $-2g_z$  step input sequence ( $> 1g/sec$ ), followed by  $\pm 2g_z$  sinusoidal accelerations from 0.005 to 1.5 Hz. The test length for each step input and each frequency lasted approximately 3 minutes. Control (no acceleration) segments were taken prior to the first step input and again prior to the first sinusoidal test. Preliminary studies showed that the "alerting response" could be eliminated if the test changes were made without bringing the centrifuge down between tests.

For the blocker studies, individual and combinations of pharmacologic blockers (Phentolamine, Atropine, and Propranolol) were then administered to each animal, producing an experimental state from which a particular neural control pathway had been removed. Fourteen experiments using 8 unblocked dogs and 2 experiments using 2 dogs in the unblocked and blocked states have been conducted to date.

## RESULTS

### Step Input Acceleration

The responses of each animal to 2 g step inputs have been studied, the uninterrupted sequence being 3 minutes each of  $+2g_y$ ,  $+2g_z$ ,  $-2g_y$ , and  $-2g_z$ , repeated at least once, each being delivered at an approximate rate of 1 g/sec. With the onset of  $+2g_z$  (Figure 3), there normally was a rapid drop in stroke volume and aortic, left ventricular, and right ventricular systolic and diastolic pressures, an instantaneous increase in heart rate followed by a slower increase in heart rate and, following that, a slow rise in peak  $dp/dt$ . This increase in  $dp/dt$  was accompanied by increases in aortic systolic and diastolic pressures, left ventricular and right ventricular systolic pressures and peak aortic flow. Following this peak in all variables, a steady state was established, operating at new mean levels for the remainder of the test period. Calculation of the classical variable, "peripheral resistance" defined as the ratio of the terms: 
$$\frac{\text{mean aortic pressure} - \text{diastolic right ventricular pressure}}{\text{stroke volume} \times \text{heart rate}}$$

from the beat to beat values of each of these variables indicated a rapid (2 sec) drop in resistance to less than half of the control values, followed by a much slower rise to near control levels accompanied by a corresponding drop in heart rate.

While the phasic response of the various cardiovascular variables to step g loadings is apparent from Figure 3, mean (nonphasic) changes and particularly the cardiac output responses are not. Consequently the phasic aortic pressure and aortic flow data from Figure 3 were digitally meaned by computer and are presented in Figure 4 along with  $g_z$  acceleration and heart rate. The ratio of mean aortic pressure to mean aortic flow (approximately equal to impedance) is also presented to provide information about the possible role of capacitance and resistance mechanisms in the cardiovascular adjustment to acceleration load-

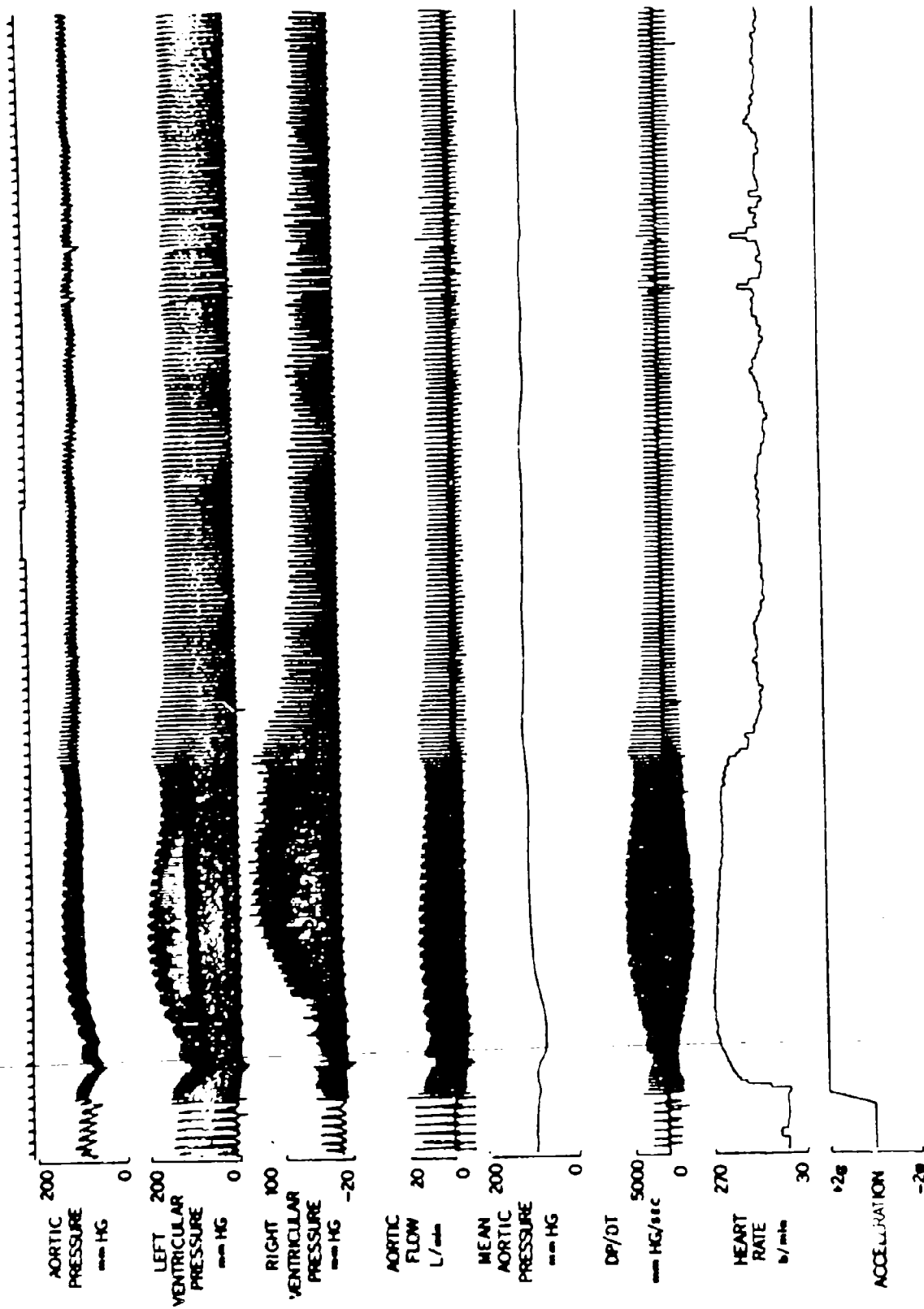


Fig. 3. Cardiovascular responses to +2  $g_z$  step input.



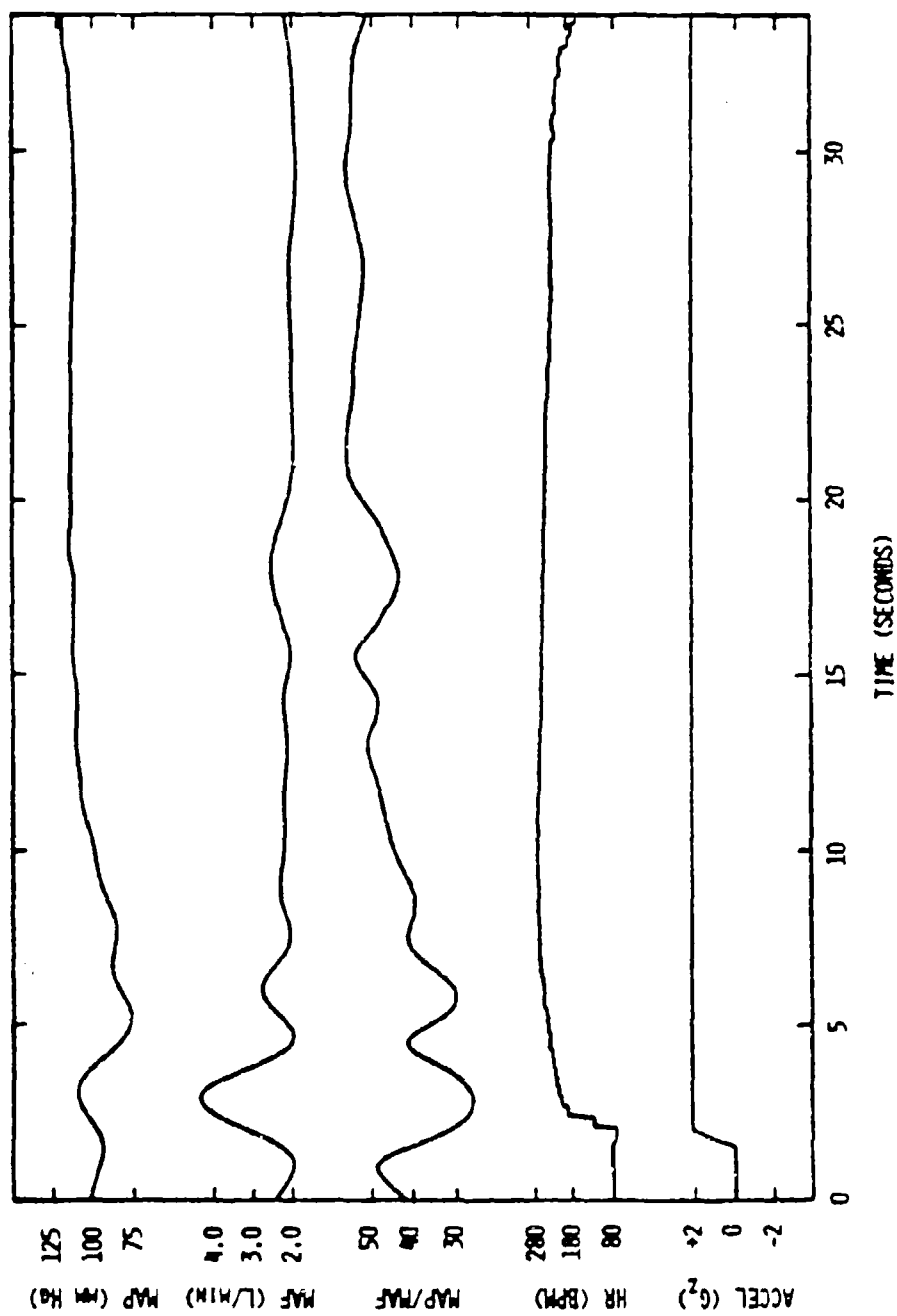


Fig. 4. Digitally meaned aortic pressure and flow responses to +2 g<sub>z</sub> step input.

ing. The initial increase in cardiac output did not cause a commensurate increase in aortic pressure, as reflected in a decreased impedance, probably due to hydraulic loading of capacitance elements in the arterial tree and a possible initial reflex dilation of the vascular beds. After 8-10 seconds cardiac output returned to a reduced level which was more or less maintained thereafter, while aortic pressure was seen to start a gradual, but steady recovery indicating an active increase in vascular resistance. The vascular adjustment was complete after 15-20 seconds.

The response of most animals to  $-2g_z$  (Figure 5) can be characterized by an instantaneous rise in all pressure variables and a transient increase in heart rate, followed by a pronounced sinus rhythm around the control value of heart rate. The digitized version of this data, shown in Figure 6, indicates an increase in mean aortic flow in spite of the 25mm Hg rise in aortic pressure. A transient decrease in aortic impedance, implying some active peripheral dilation, would appear to account for this phenomena. Throughout the remainder of the test, an oscillatory impedance accompanied the flow and pressure oscillations. A steady state for all variables appeared to be established in less than 15 seconds following this type of input.

Interestingly, the transient response to  $+2g_y$  (following 3 minutes of  $-2g_z$ ) was almost identical to the transient response to  $+2g_z$ , but a return to control levels (no acceleration) was reached in approximately 15 seconds. In a similar manner, the transient response to  $-2g_y$  (following 3 minutes of  $+2g_z$ ) was like that of the transient response to  $-2g_z$ , again returning rapidly to control levels. These transient responses are thought to indicate the baroreceptor response to rising or falling arterial and venous pressures, without the steady state response produced by the appropriate  $g_z$  step input.

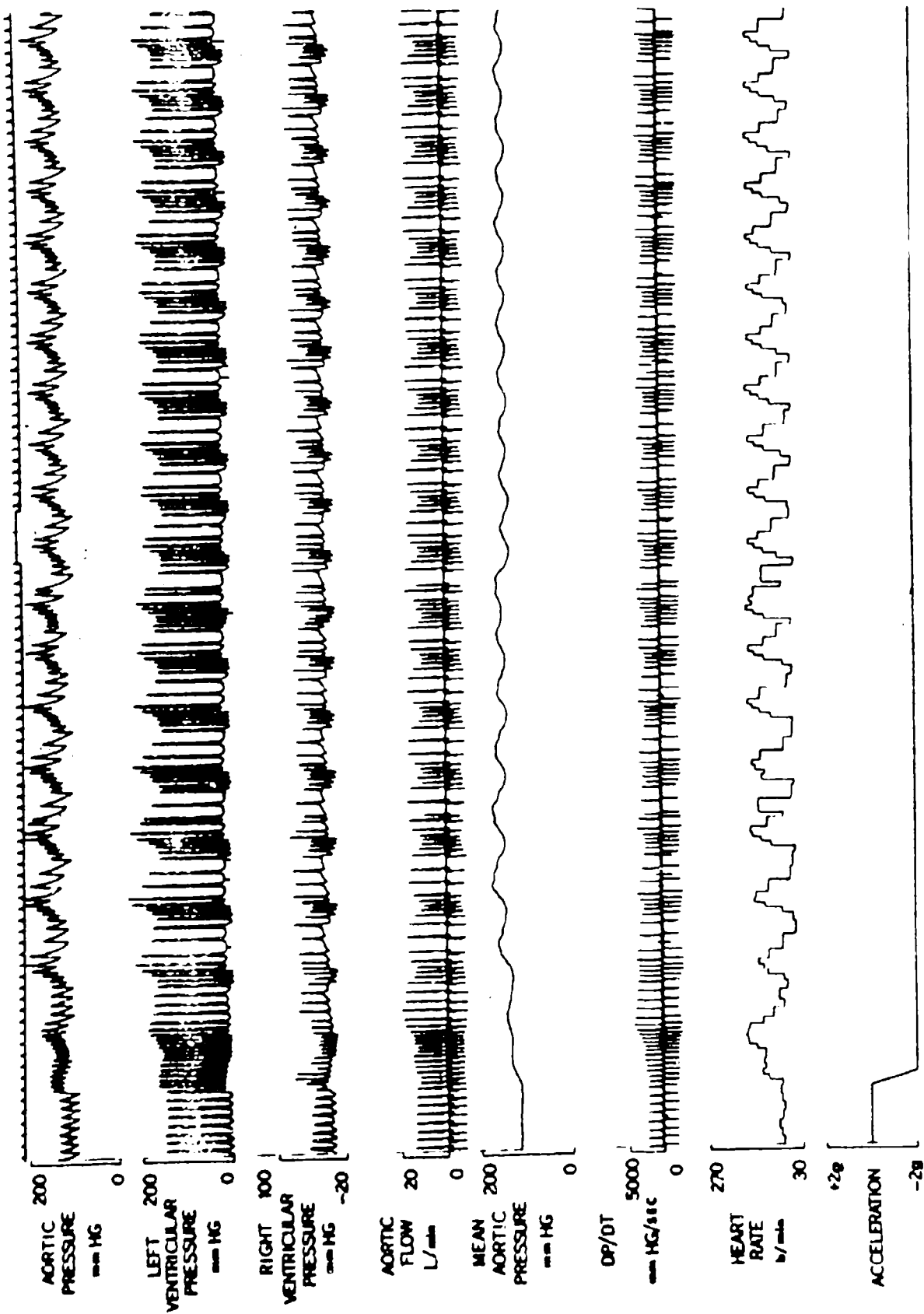


Fig. 5. Cardiovascular responses to  $-2 g_z$  step input.

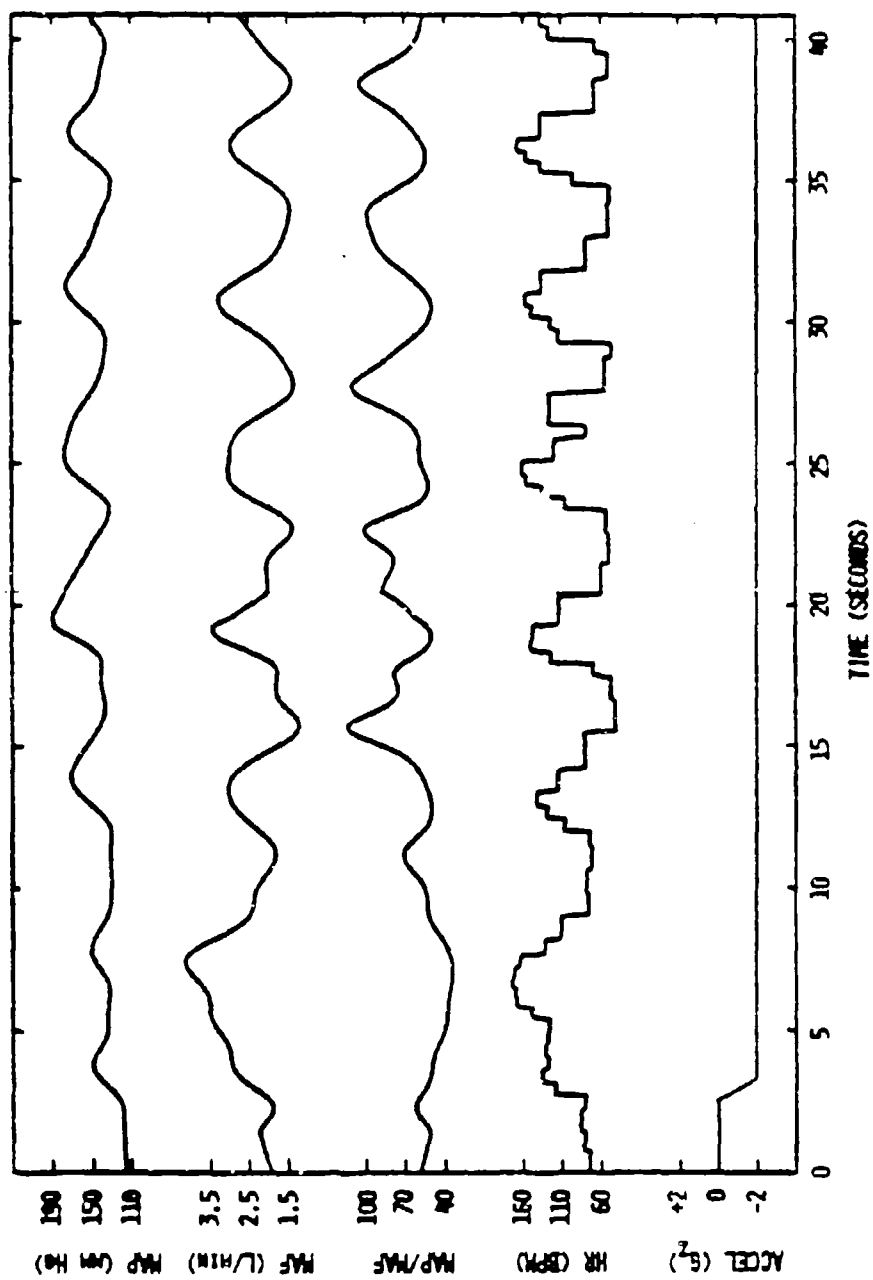


Fig. 6. Digitally meaned aortic pressure and flow responses to  $-2 g_z$  step input.

### Sinusoidal Acceleration

Typical responses of one animal to  $\pm 2g_z$  sinusoidal acceleration at frequencies from 0.025 to 0.33 Hz is shown in Figure 7. Each of the seven segments of data presented represent steady state responses to a particular acceleration loading. The loadings were produced sequentially, starting with the low frequency, and lasted  $\sim 3$  minutes each (no recovery periods between tests).

For the sinusoidal acceleration loading at a frequency of .025 Hz, aortic pressure, left ventricular pressure, right ventricular pressure, peak aortic flow, and left ventricular dp/dt decreased as acceleration reached  $+ 2g_z$  (blood to the tail). Heart rate increased as acceleration approached  $+ 2g_z$  and continued to increase several seconds after the peak acceleration was reached. As  $-g_z$  acceleration was applied (blood to the head) the heart rate response decreased dramatically reaching its minimum value prior to the peak values of  $- 2g_z$ . The other variables showed various rates of increase in response to the  $- 2g_z$  acceleration loading and the compensatory heart rate adjustments.

When each response is examined as a function of increasing acceleration frequency (for constant  $\pm 2g_z$  amplitude), the following observations can be made from Figure 7. The amplitude of the heart rate oscillations decreased with increasing acceleration frequency. For an acceleration frequency of 0.33 Hz, no significant heart rate oscillations were obvious. Over the same acceleration frequency range, the amplitude of the aortic pressure oscillations did not decrease as rapidly as did those of heart rate. Accompanying the decrease in aortic pressure amplitude, was an increase in the mean value of aortic pressure at the higher acceleration frequencies. The oscillations in right ventricular pressure were large and did not decrease with increasing frequency. The oscillations which occurred in the left ventricular pressure and dp/dt responses, and peak aortic flow responses all tended to decrease with increasing acceleration frequency.

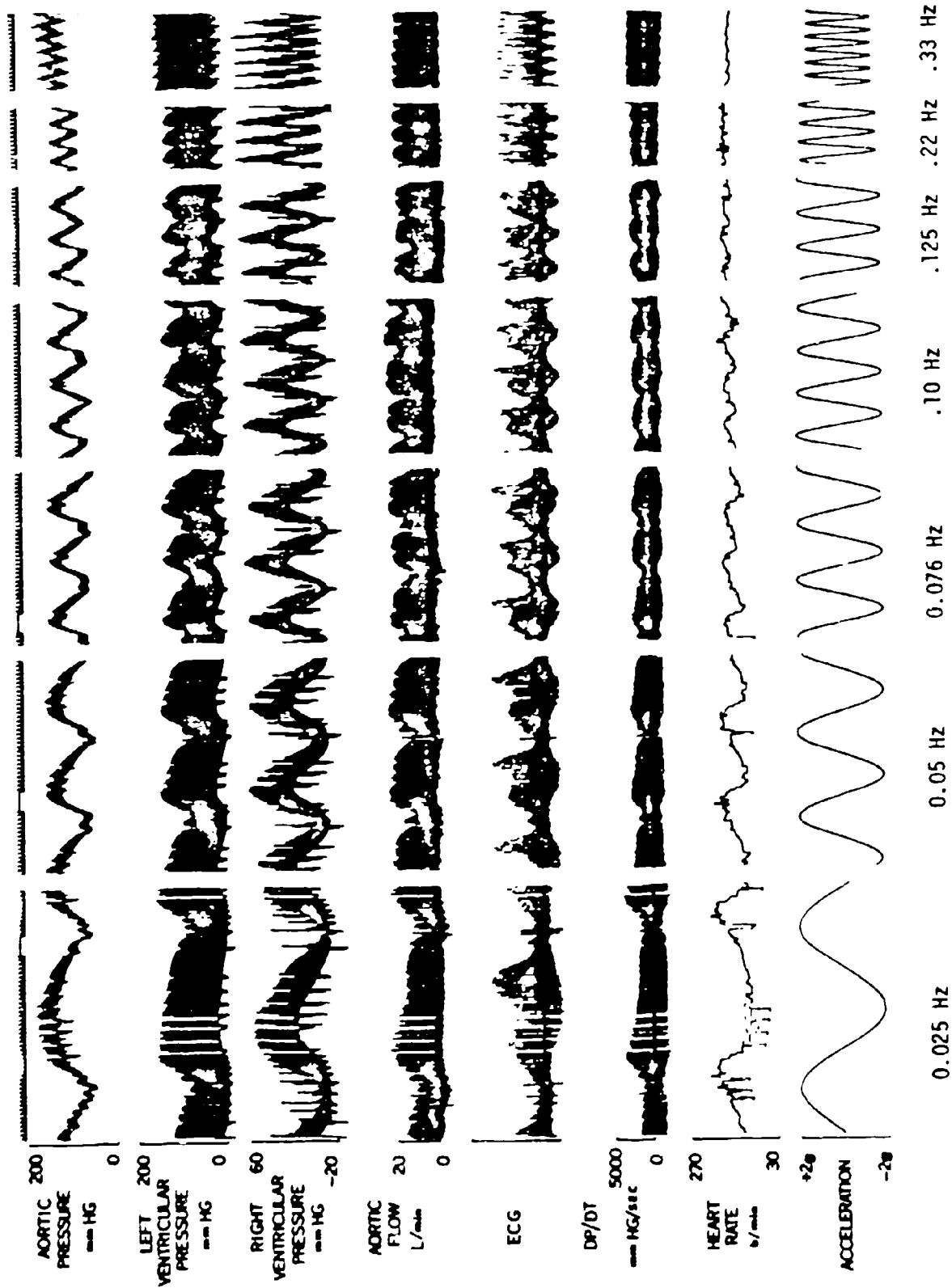


Fig. 7. Cardiovascular responses to sinusoidal acceleration of constant  $+2 g_z$  amplitude.

Each of the responses is being examined in detail with respect to its amplitude and phase relationship to the acceleration input as well as its relationship to other companion cardiovascular variables.

This report will deal primarily with heart rate and aortic pressure responses to sinusoidal acceleration loadings. An example of the analysis currently in progress is shown in the sequence of Figures 8-13. The heart rate response is used as the example variable. The analysis is designed to answer the following questions: Is there any portion of the heart rate response correlatable with the acceleration input? This question is then further divided into several parts. First, is there any periodicity in the heart rate trace that has the same frequency as that of the acceleration? And, is the periodicity consistent throughout the test period? Second, how do the amplitudes of the heart rate oscillations, which are correlatable with those of the acceleration input, vary over the frequency range tested? And third, what is the phase relationship between the heart rate and acceleration oscillations?

In Figure 8, the frequencies of the heart rate oscillations were measured and compared to the frequencies of the acceleration oscillations. These data are from 12 experiments on six days using three different dogs. In almost every case, the frequency of the heart rate oscillations was the same as the frequency of the acceleration input up to 0.3 Hz. For frequencies greater than 0.3 Hz the following was observed: 1) the amplitudes of the heart rate oscillations were so small that it was difficult to ascertain a particular frequency that could be related to the input frequency, or 2) the heart rate oscillations were large but the frequency was inconsistent or did not relate to the input frequency. In order to quantify the responses in the area of 0.3 Hz and beyond, a computer analysis was used, the results of which are shown in Figures 9, 10, and 11. Figure 9 shows digitized traces ( $\sim 60$  ms digitizing rate) for the control condition, an acceleration frequency of 0.2 Hz for which the heart rate oscillations

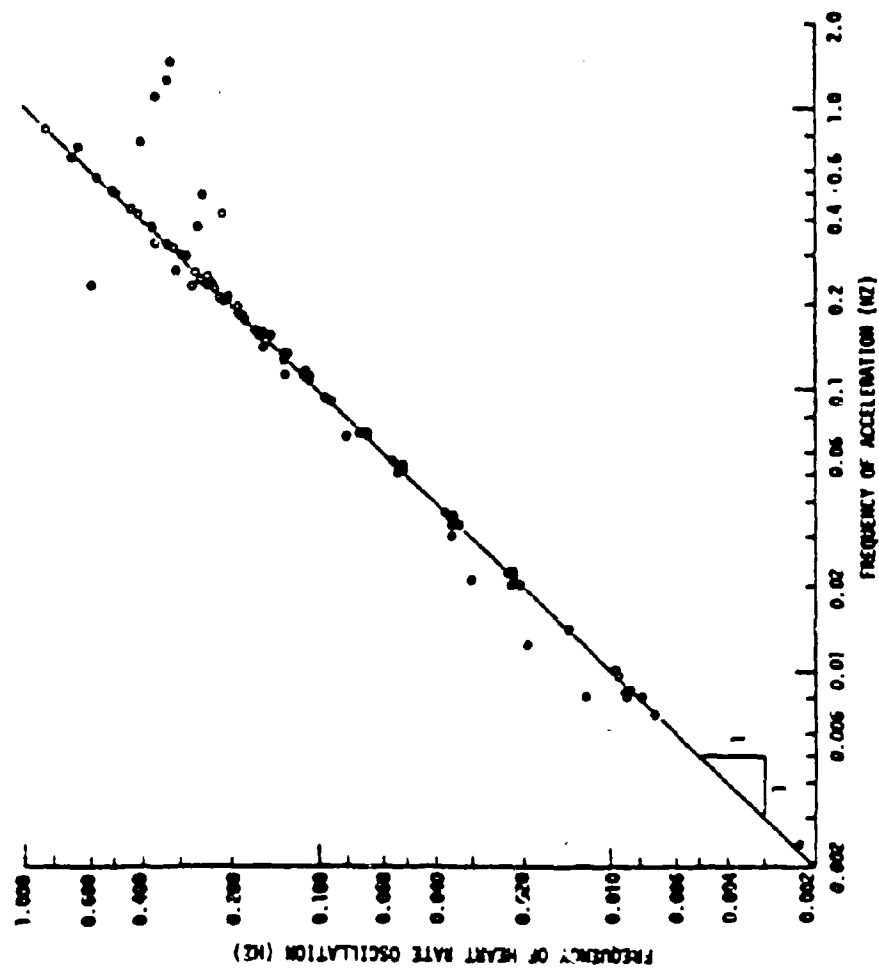


Fig. 8. Frequency of acceleration-induced heart rate oscillations versus frequency of acceleration; 3 subjects, 12 tests on 6 days, at  $\pm 2 g_z$ .



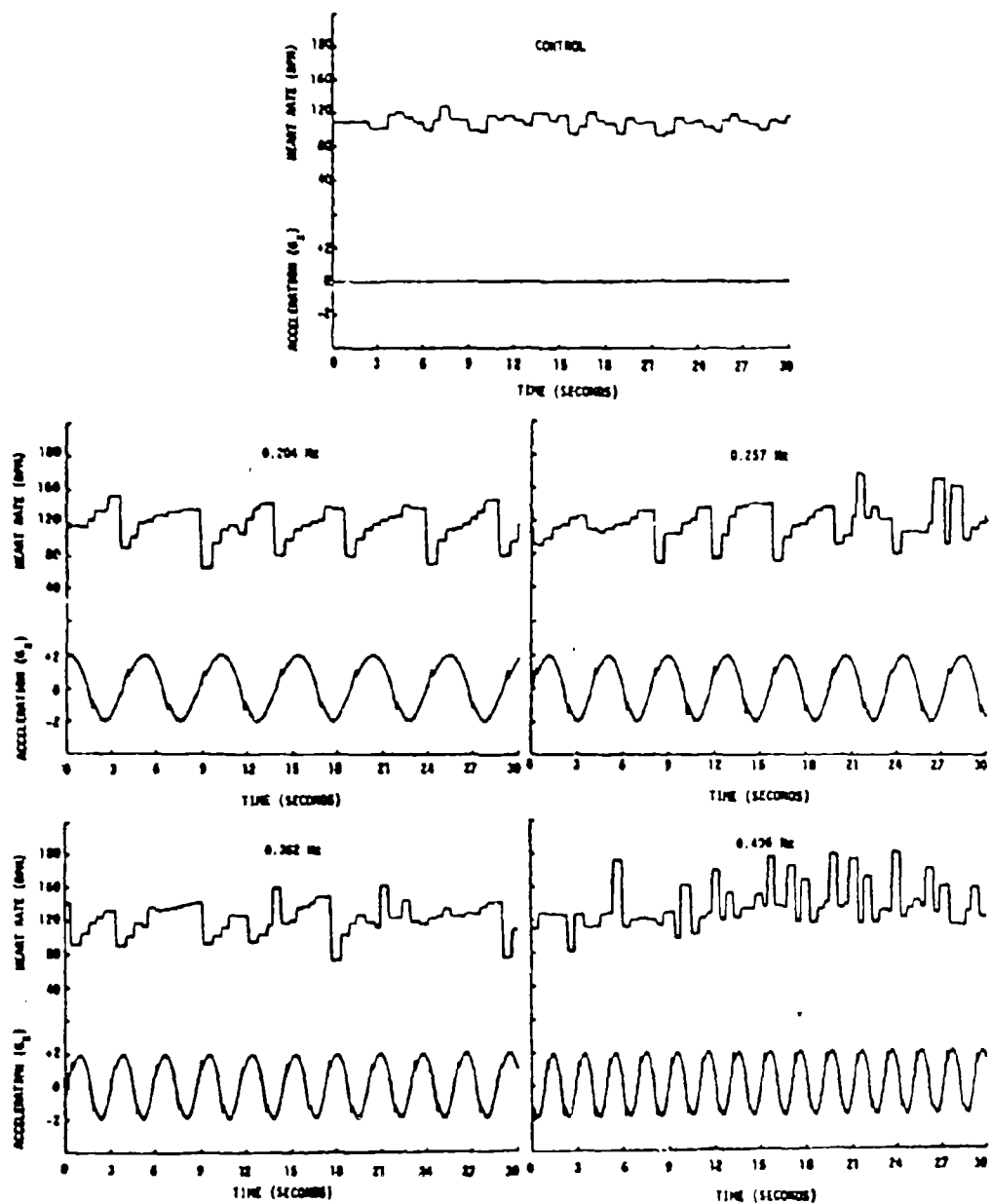


Fig. 9. Simultaneously digitized data record of  $g_z$  input acceleration and heart rate for a control period, and four discrete input acceleration frequencies ( $\sim 60$  ms sampling).

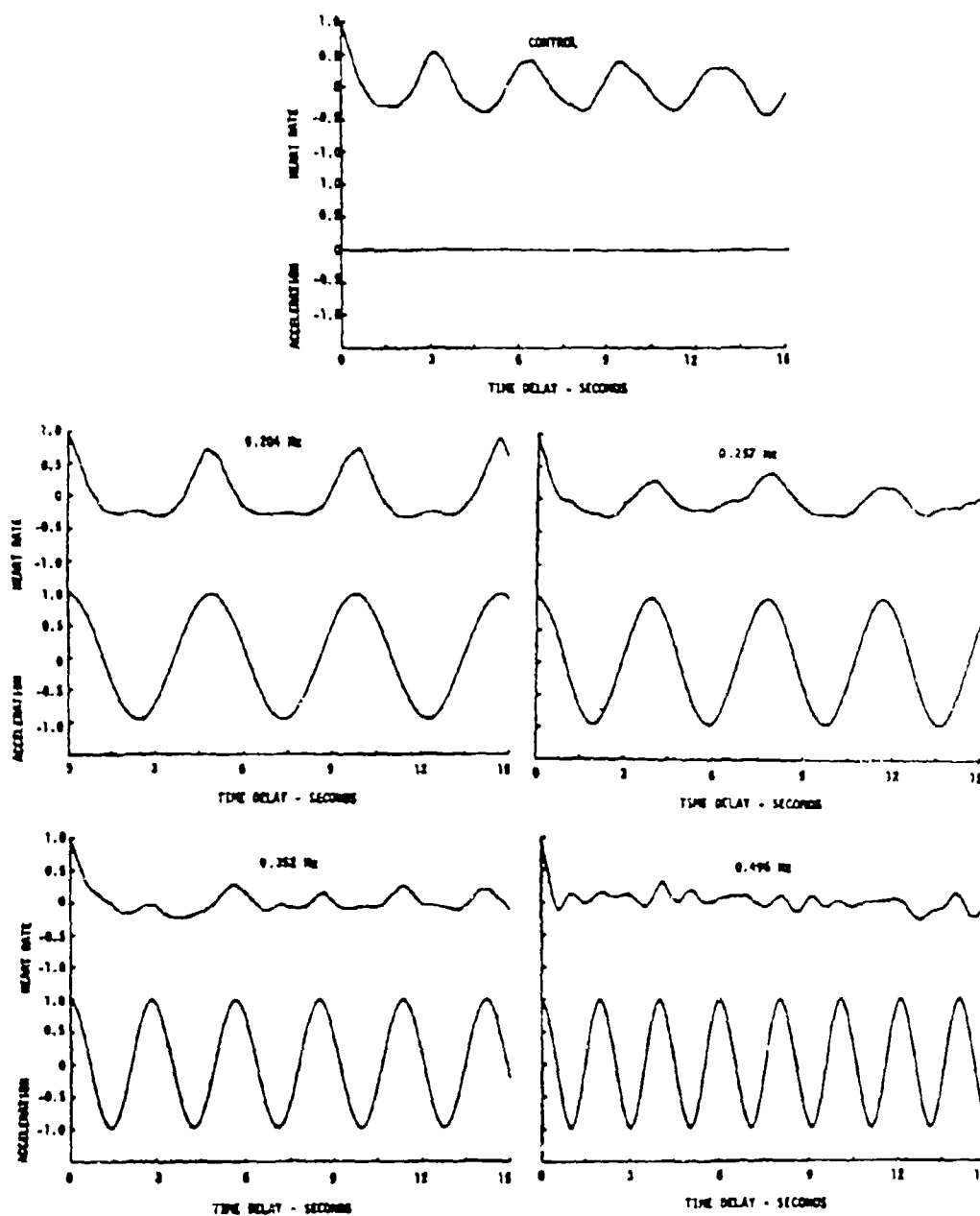


Fig. 10. Normalized auto-correlation function of the acceleration and heart rate records shown in fig. 9 for time delays of 0.0 to +15.0 seconds.

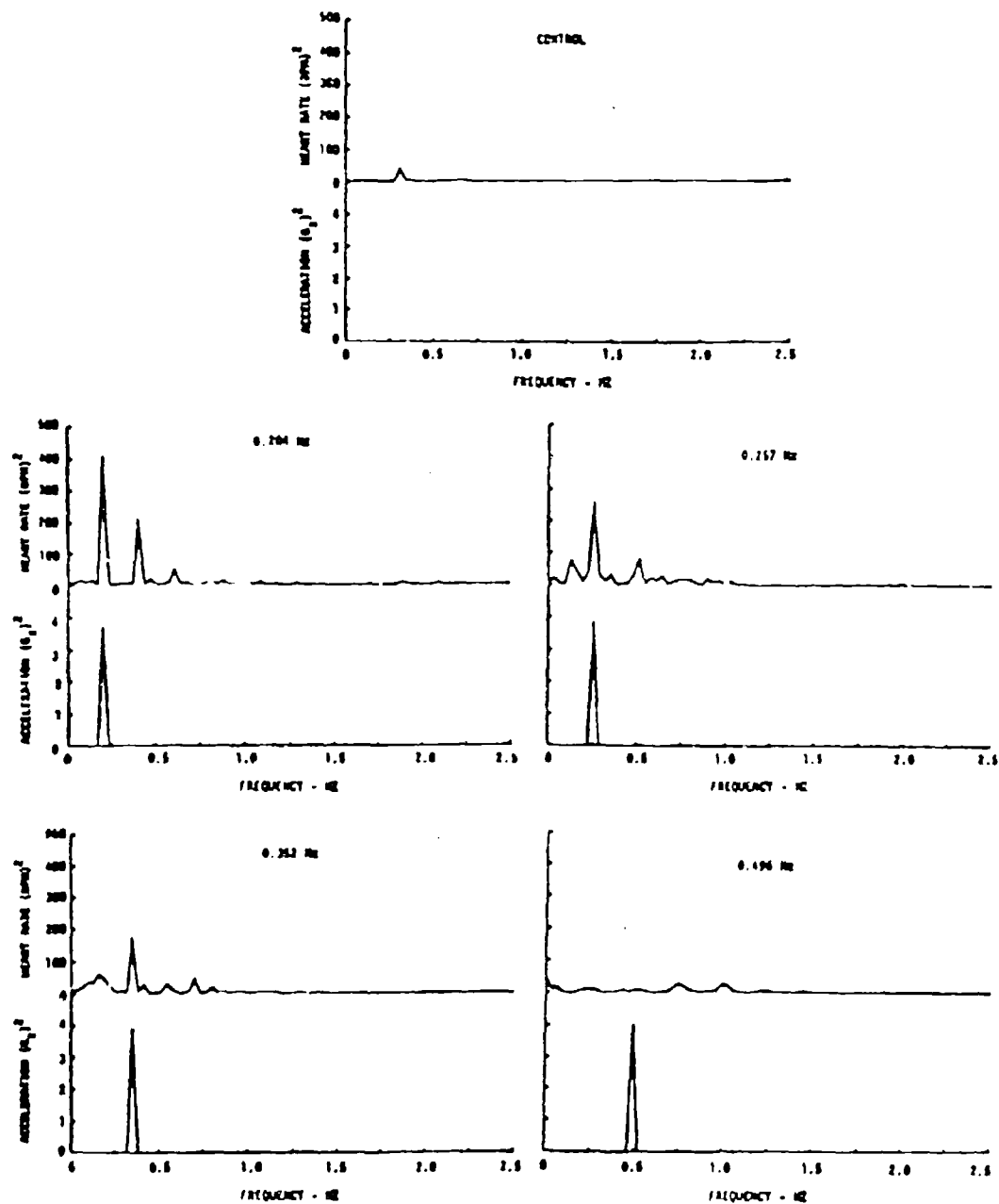


Fig. 11. Power spectral estimates of the acceleration and heart rate records shown in fig. 9.

clearly followed, and three other frequencies (0.25, 0.35 and 0.5Hz) for which the heart rate oscillations become less consistent throughout the test period. The autocorrelations of both the heart rate and acceleration traces are presented in Figure 10. The degree to which each signal approximates a cosine function is an indication of the strength of the periodicity of the signal. The quality of the heart rate autocorrelation function is seen to deteriorate with increasing frequency. In order to get a more objective measure of the decline in heart rate response after 0.3 Hz, the power spectral density of the signal was analyzed and plotted in Figure 11. In this figure, the power spectra of the heart rate signal and acceleration signal are shown for control and the four frequencies chosen for analysis. It is clear that the fundamental frequency of the heart rate response is the same as that of the input acceleration for the first three frequencies. It may also be observed that the amplitude of the power spectrum decreases with increasing frequency until at 0.5 Hz no correlation between acceleration and heart rate response can be observed.

The power spectral estimates as shown in Figure 11 can be calculated for all the frequencies tested and are presented in the contour plot of Figure 12. The spectral frequencies of the heart rate response are plotted on the x axis and the frequency of the acceleration loadings are plotted on the y axis. The height of the spikes which project vertically above the xy plane represents the squared amplitude of the spectral peaks in units of  $(\text{beats/min})^2$ . The solid line running diagonally across the graph represents the location of constant amplitude spikes resulting from the input acceleration. For a given input acceleration, the first spike represents the power of the fundamental; the second spike represents the power of the second harmonic and so on. It is clear from this contour plot that the fundamental frequency of the heart rate response is the same as that of the input acceleration up to frequencies of about 0.5 Hz,

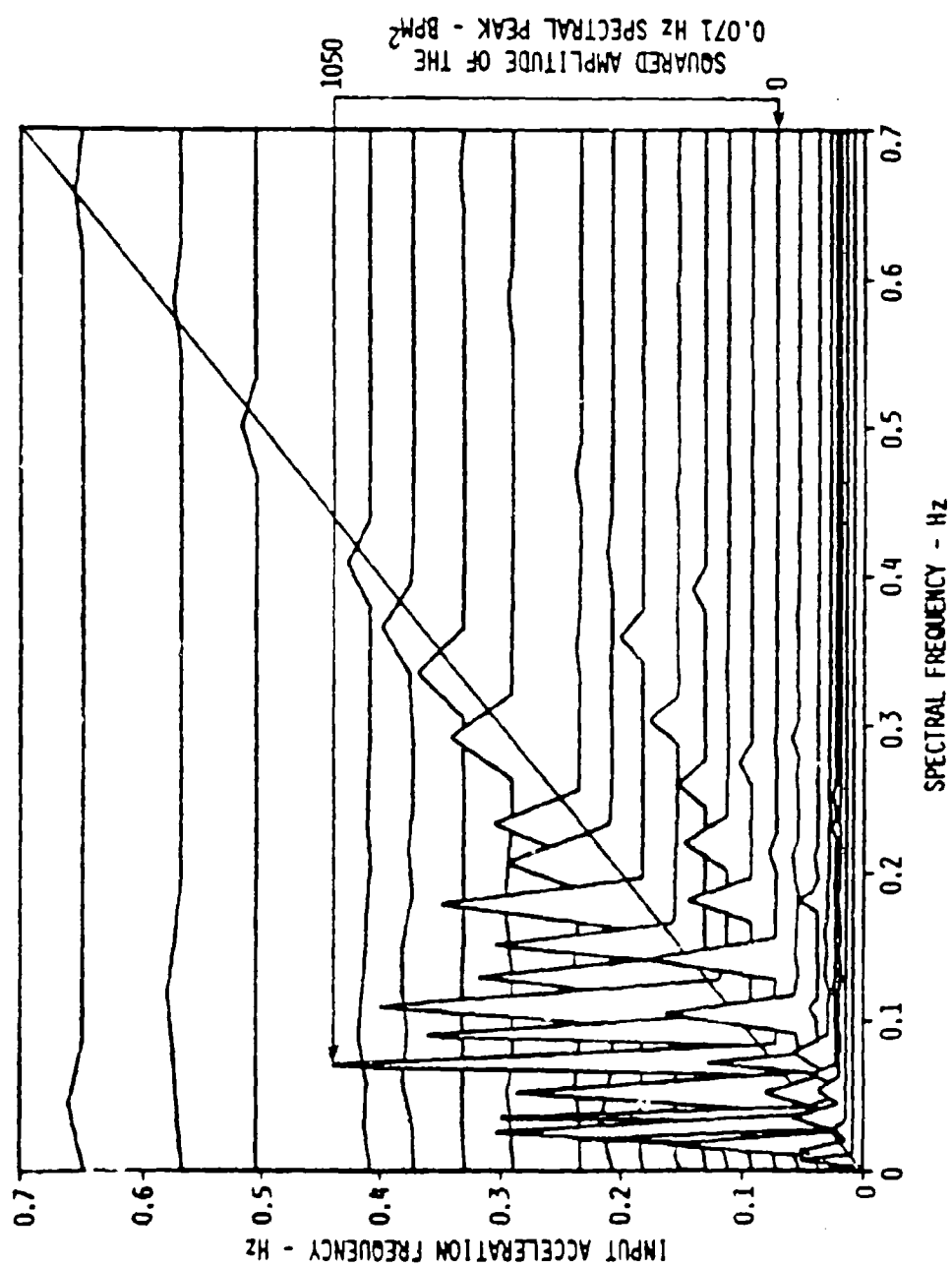


Fig. 12. Spectral map of heart rate response to 0.008-0.650 Hz,  $\pm 2 g_z$  acceleration.

with the most power occurring for acceleration frequencies between 0.02 Hz and 0.1 Hz. A slice through the contour plot along the diagonal line representing the input acceleration frequencies, can provide a clearer picture of the amplitude of the harmonic components and their phase relationship to the acceleration input. These data are shown in Figure 13. The spectral amplitudes of the fundamental and second harmonic components of the heart rate response are shown in the middle of the figure. The phase relationship of the fundamental component of the heart rate response to the fundamental component of the input acceleration is shown at the bottom of Figure 13. The heart rate response is seen to lead the acceleration input up to a frequency of 0.055 Hz and then lag for higher values of acceleration frequency. The lead of the heart rate response for the low acceleration frequencies is due primarily to the system's ability to rapidly decrease heart rate well in advance of the  $-2g_z$  peak acceleration loading, even though the heart rate increase lags behind the rise to the  $+2g_z$  acceleration peak (Figure 7).

The mean heart rate over the entire test period for each frequency is shown in the upper portion of the figure. The mean values initially decreased with increasing frequency and then rose for acceleration frequencies above 0.04 Hz.

Further insight into the nature of the heart rate response can be achieved by investigating the way in which changes in the amplitude of the oscillation were produced. In the upper half of Figure 14 the absolute values of the maximum and minimum heart rate responses for each acceleration frequency tested are shown for the same animal data as that in Figure 13. Each value represents the average over the test period, as indicated by the insert of a typical response, shown on the right side of the figure. The difference in the two values, i.e. the amplitude of the heart rate oscillations, is shown in the lower half

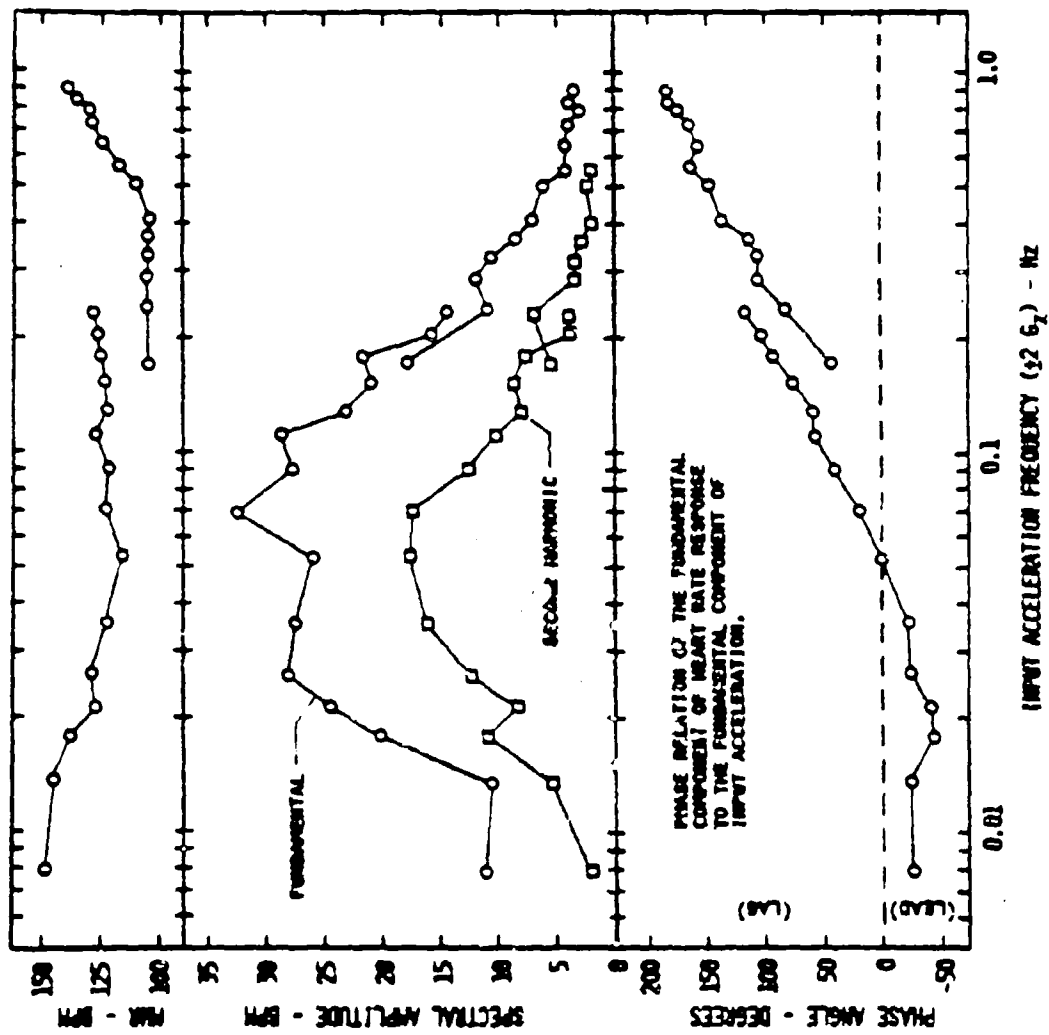


Fig. 13. Mean heart rate, spectral amplitude and phase angle versus acceleration frequency. [Break in data due to a centrifuge shutdown (~15 min) to change gear boxes]

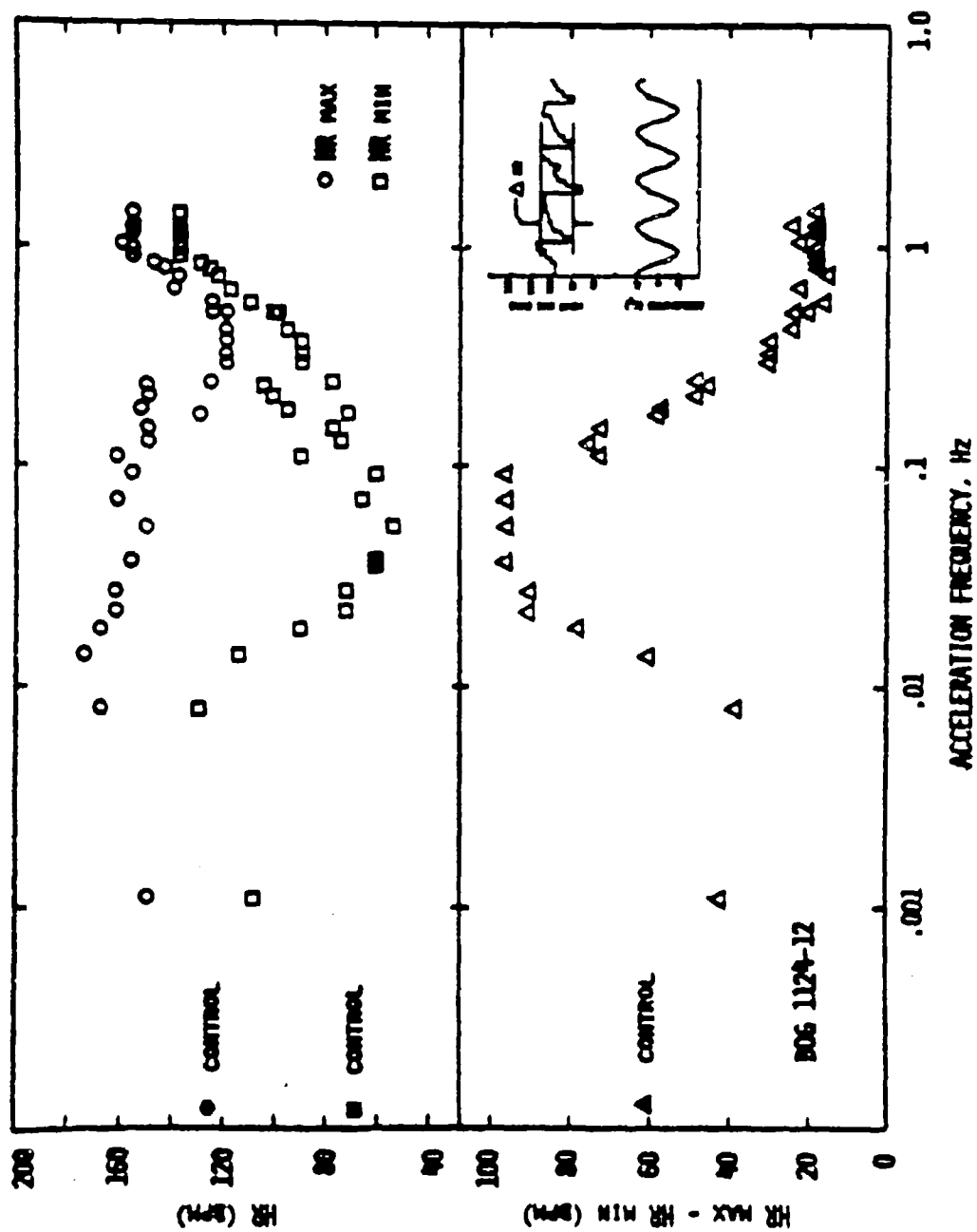


Fig. 14. Heart rate max. and min., and difference versus acceleration frequency.



of the figure. The shape of this curve, which represents the combined amplitude of all the spectral components in the heart rate, is similar to the one shown in Figure 13, which represents the amplitude of the fundamental and second harmonic components of the heart rate response only. The oscillations are maximal between acceleration frequencies of 0.02 and 0.1 Hz. The increase and then decrease of the heart rate oscillations as a function of frequency results primarily from the minimum heart rate reached during any test frequency as illustrated in the upper half of the figure, i.e. the minimum heart rate seen changed considerably more over the frequency range tested than did the maximum heart rate seen.

Aortic pressure was analyzed in a manner similar to that used for the heart rate response. The results of one animal, which are typical of all animals tested, are shown in Figure 15. The maximum and minimum mean aortic pressure values for each acceleration frequency tested are shown in the top portion of the figure. The differences in these two values, i.e. the amplitude of the mean aortic pressure oscillations for each acceleration frequency tested are shown in the bottom portion of the figure. The maximum oscillations in aortic pressure are seen to occur between acceleration frequencies of 0.035 and 0.06 Hz. The excursions in mean aortic pressure are due primarily to changes in the minimum values as shown in the upper portion of the figure. Maximum mean aortic pressures remain relatively constant throughout the frequency range. However, the mean of these aortic pressure oscillations initially decreased for acceleration frequencies up to approximately 0.04 Hz and then began to increase for higher values.

The frequency response of each of the variables measured in these experiments is currently being analyzed in the same manner described above. Details of these analyses will be included in future progress reports. However, with

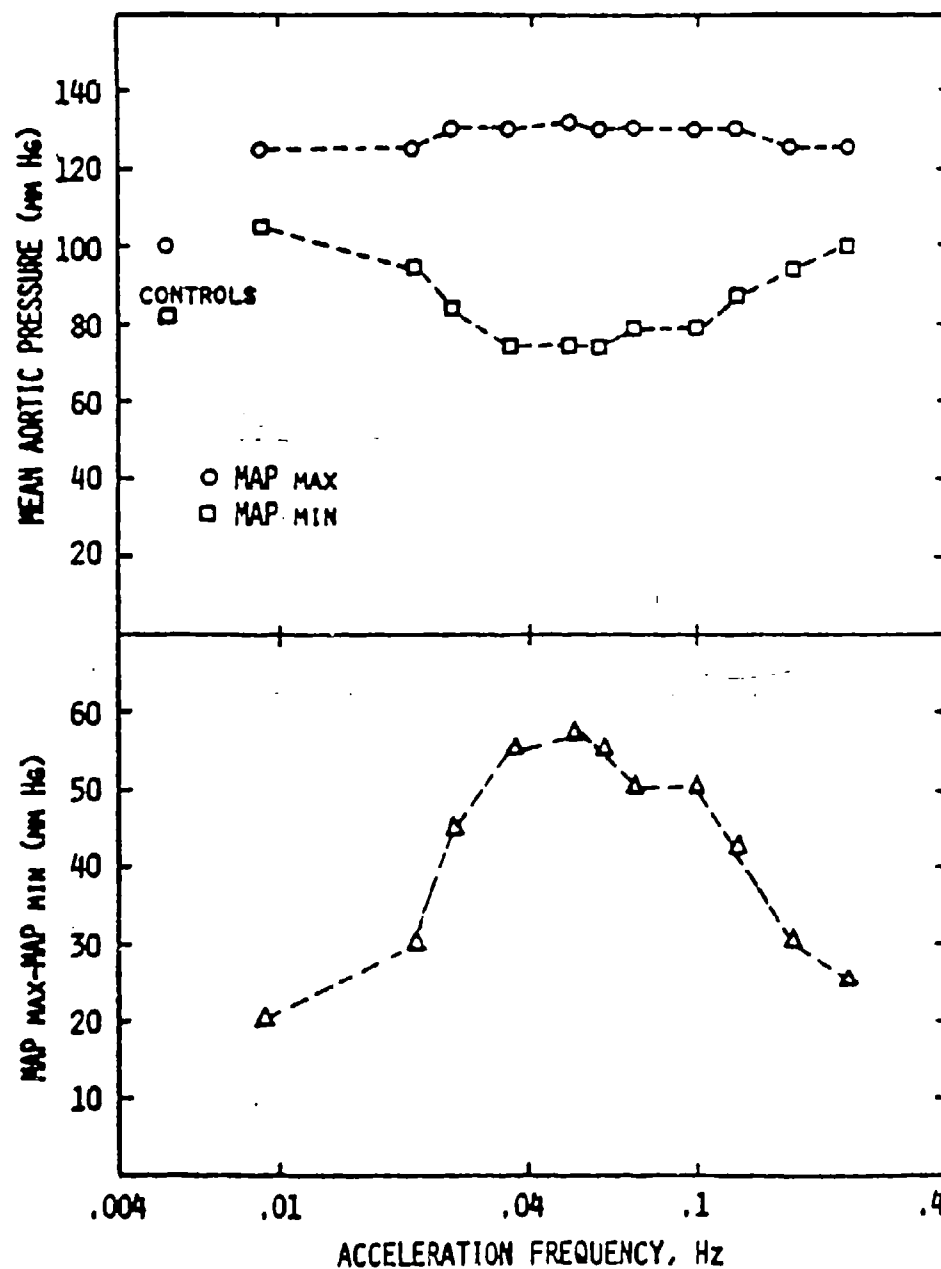


Fig. 15. Mean aortic pressure max. and min., and difference versus acceleration frequency.

the data collected to date, several inquiries concerning the relationship of the heart rate response to the acceleration loadings are in order. An initial question concerns the consistency of the acceleration forcing function. With the acceleration amplitude maintained constant throughout the experiment ( $\pm 2g_z$ ), does the amplitude of the actual pressure disturbance seen by the cardiovascular system remain constant throughout the frequency range? Initially the only information we had concerning this question was data from a freshly sacrificed animal exposed to the same acceleration amplitudes and frequency range used in this study. The pressure disturbances in the arterial and venous side, while a little different in amplitude from each other, remained relatively constant throughout the frequency range. The waveform of the acceleration disturbance was asymmetrical, i.e. blood to the head produced a larger increase in pressure than blood to the tail produced a decrease in pressure. The shape of the disturbance waveform also changed as the frequency increased, but the peak to peak values remained relatively unchanged. The degree to which volume shifts could be produced at the very low frequencies could not be assessed with this experimental preparation. The extent to which pressure disturbances in the freshly sacrificed animal represented those in the intact passive hydraulic animal was also not clear.

Therefore, to investigate the nature of the pressure disturbances produced by the acceleration loadings only, a series of experiments using pharmacologic blocking agents was initiated. Since the data presented below is from only one animal, the results must be considered highly preliminary. However, they are included to illustrate the type of responses anticipated in the coming year. In order to look at the "opened loop", (purely hydraulic) pressure disturbances produced by time dependent acceleration loadings, both cardiac and peripheral vascular feedback mechanisms had to be inactivated. Chronotropic and inotropic cardiac mechanisms were blocked with a combination of atropine, a parasympathetic

cholinergic blocker, and propranolol, a beta adrenergic blocker. Peripheral vascular mechanisms were blocked by the administration of phentolamine, an alpha adrenergic blocker. Examples of the cardiovascular responses of the same animal to a single frequency (0.039 Hz) for the normal and each blocked state are shown in Figure 16. The normal and "hydraulic" responses of another animal to a different frequency (0.075 Hz) when blocked with all three drugs are shown in Figure 17. An analysis of the individual blocker studies which will aid in delineating the relative contribution of peripheral vascular and cardiac mechanisms is beyond the scope of this progress report. A detailed analysis is currently underway. Our attention will be focused only on the aortic pressure and heart rate responses of the totally blocked animal in order to quantify the "open loop" pressure disturbances which initially drive the carotid sinus receptors. The maximum and minimum mean aortic pressure values for each acceleration frequency tested are shown in the top portion of Figure 18.

The cross-hatched area represents the envelope of the mean pressure excursions of the unblocked animal. The difference in the maximum and minimum pressure changes, i.e. amplitude of the pressure oscillations for the unblocked dog is plotted in the lower portion of the figure and represented by the dotted line. The envelope of the maximum and minimum mean pressure changes as a function of acceleration frequency for the totally blocked animal is shown by the two solid lines connecting the data points in the upper portion of the figure. The amplitude of the mean pressure oscillations for the totally blocked animal is shown in the lower portion of the figure and represented by the solid line. The amplitude of the mean aortic pressure disturbances for the totally blocked animal is seen to decrease with increasing acceleration frequency even though the acceleration amplitude remains constant. To obtain an indication of the frequency response of the integrated cardiac reflex, the heart rate response of the intact animal and the "opened

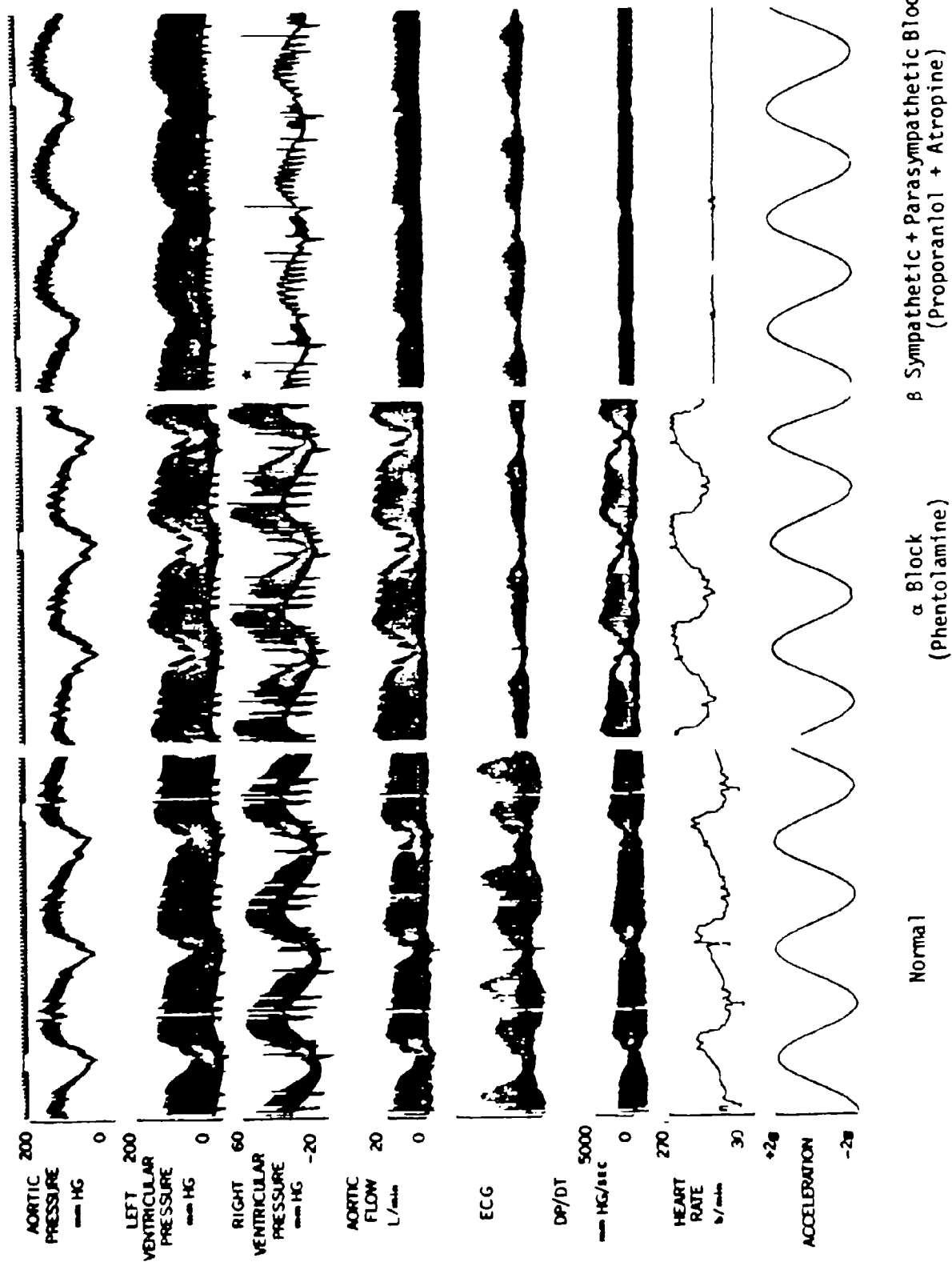


Fig. 16. Cardiovascular responses of the same animal to sinusoidal acceleration at 0.039 Hz. (\*pressure gauge in right atrium)

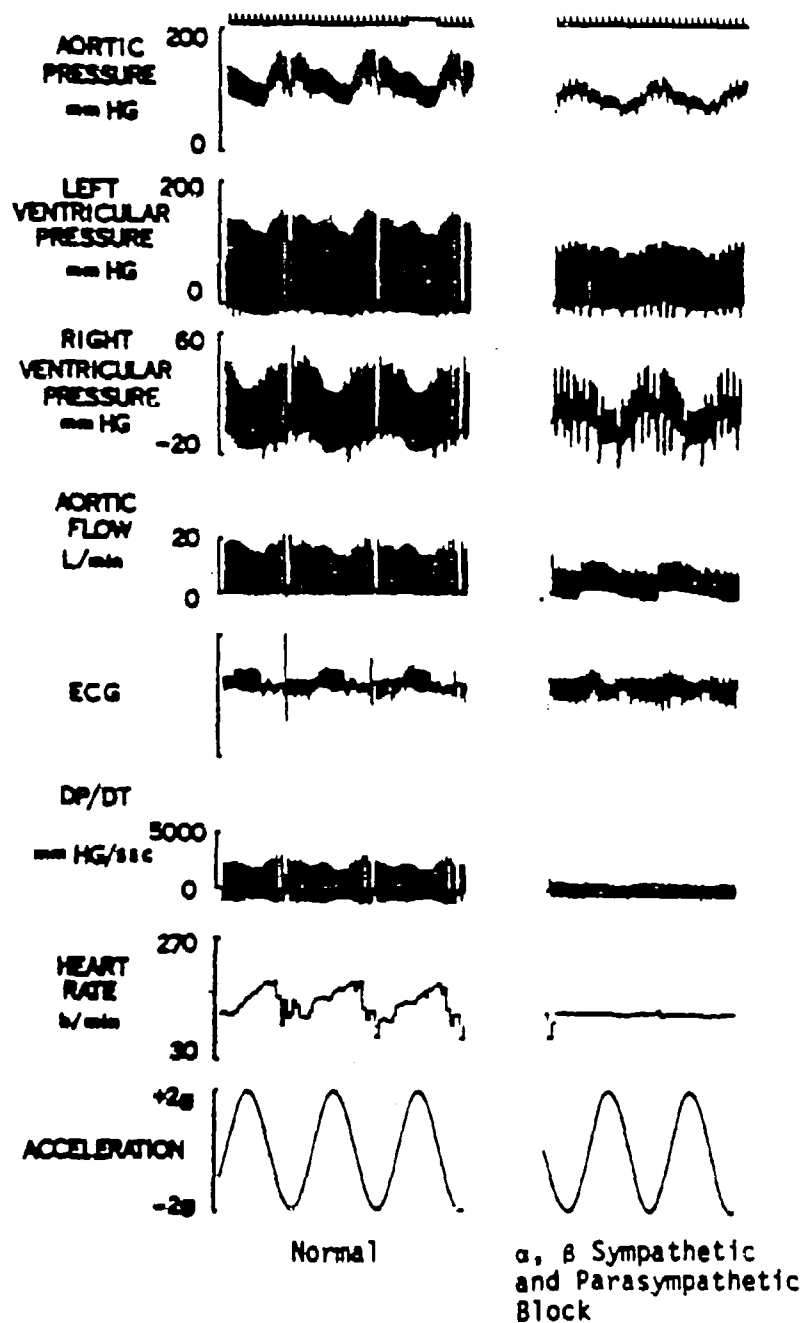


Fig. 17. Cardiovascular responses to sinusoidal acceleration at 0.075 Hz.

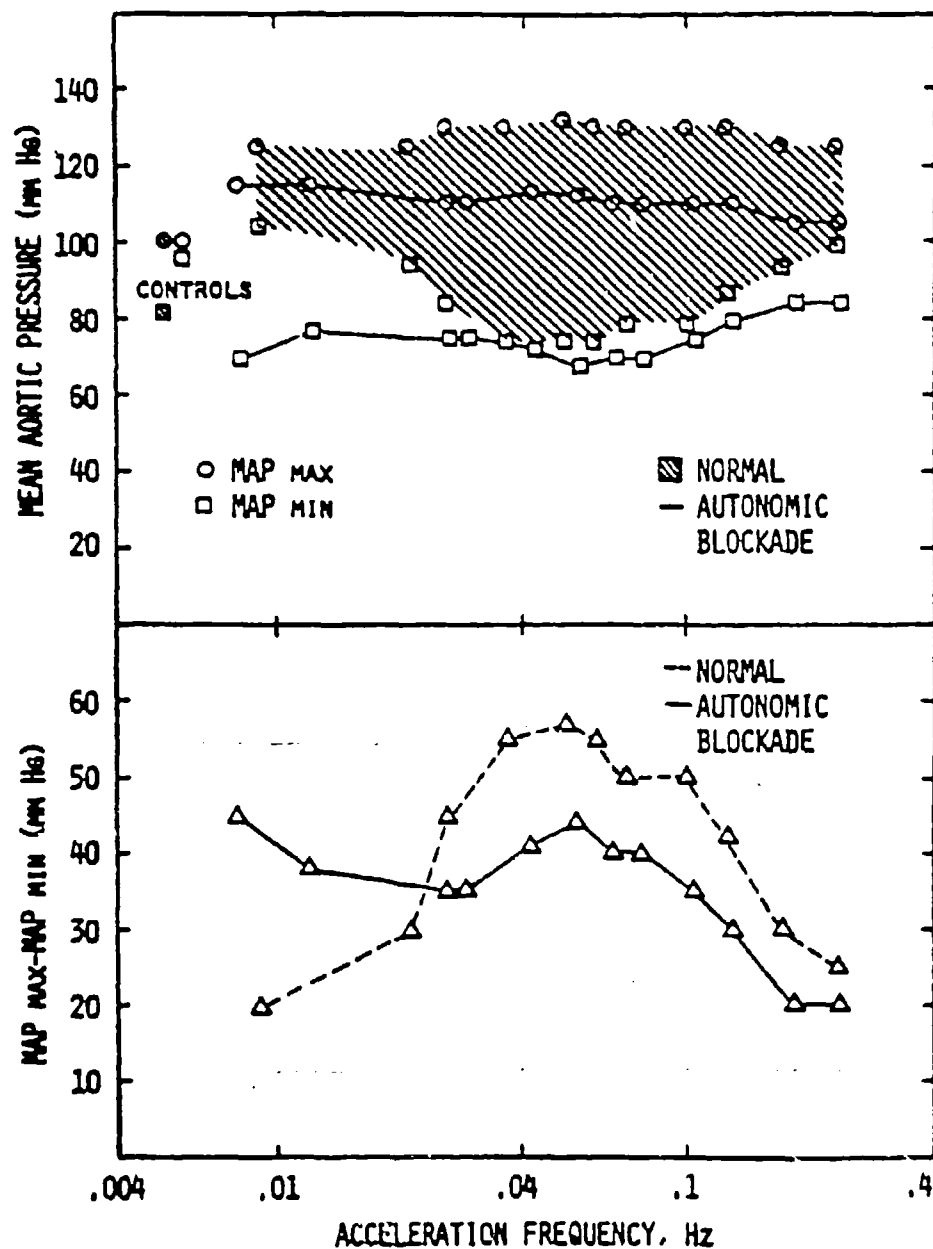


Fig. 18. Mean aortic pressure, max. and min., and difference versus acceleration frequency. (normal and total autonomic blockade)

loop" aortic pressure response for the same animal is presented in Figure 19. The ratio of these two variables, i.e. heart rate unblocked/ $\Delta P$  totally blocked, represents the "gain" of the baroreceptor cardiac reflex. These results indicate that the amplitude of the heart rate oscillations decreases more rapidly as a function of acceleration frequency than does the amplitude of the mean aortic pressure disturbances. Therefore, the gain is seen to decrease rapidly after an acceleration frequency of approximately 0.03 Hz.

A preliminary attempt to establish the frequency response of peripheral constriction and/or dilation has resulted in plots of peripheral resistance as a function of frequency (Figure 20). Resistance was calculated for the mean of each of the following variables over the three minutes spent at each frequency:

$$\text{Mean peripheral resistance} = \frac{\text{Aortic pressure} - \text{Right atrial pressure}}{\text{Stroke volume} \times \text{Heart rate}}$$

At the lower frequencies, care was taken to average the values over complete cycles. The results of these plots indicated that at frequencies below 0.05 Hz, peripheral resistance was significantly increased over the control value, but that it decreased with increasing frequency such that it was significantly below normal above 0.1 Hz. A tentative explanation for this phenomenon could be in unequal time constants for dilation as opposed to constriction, with dilation having a shorter time constant than constriction.

In preliminary studies which included first the normal animal, next the  $\alpha$  blocked animal, next the  $\beta$  plus parasympathetically blocked animal and then the totally blocked animal, it was found that the normal animal never exceeded the extremes of peripheral dilation shown with the  $\alpha$  blockade, nor the extremes of peripheral constriction reached with the  $\beta$  blockade. It further showed the increase in peripheral resistance below .05 Hz to be under the control of the  $\alpha$  sympathetic system. In the one totally blocked animal, peripheral resistance was well within the limits set by the previous  $\alpha$  and  $\beta$  + p.s. tests, responding remarkably like the normal animal across the entire frequency range.



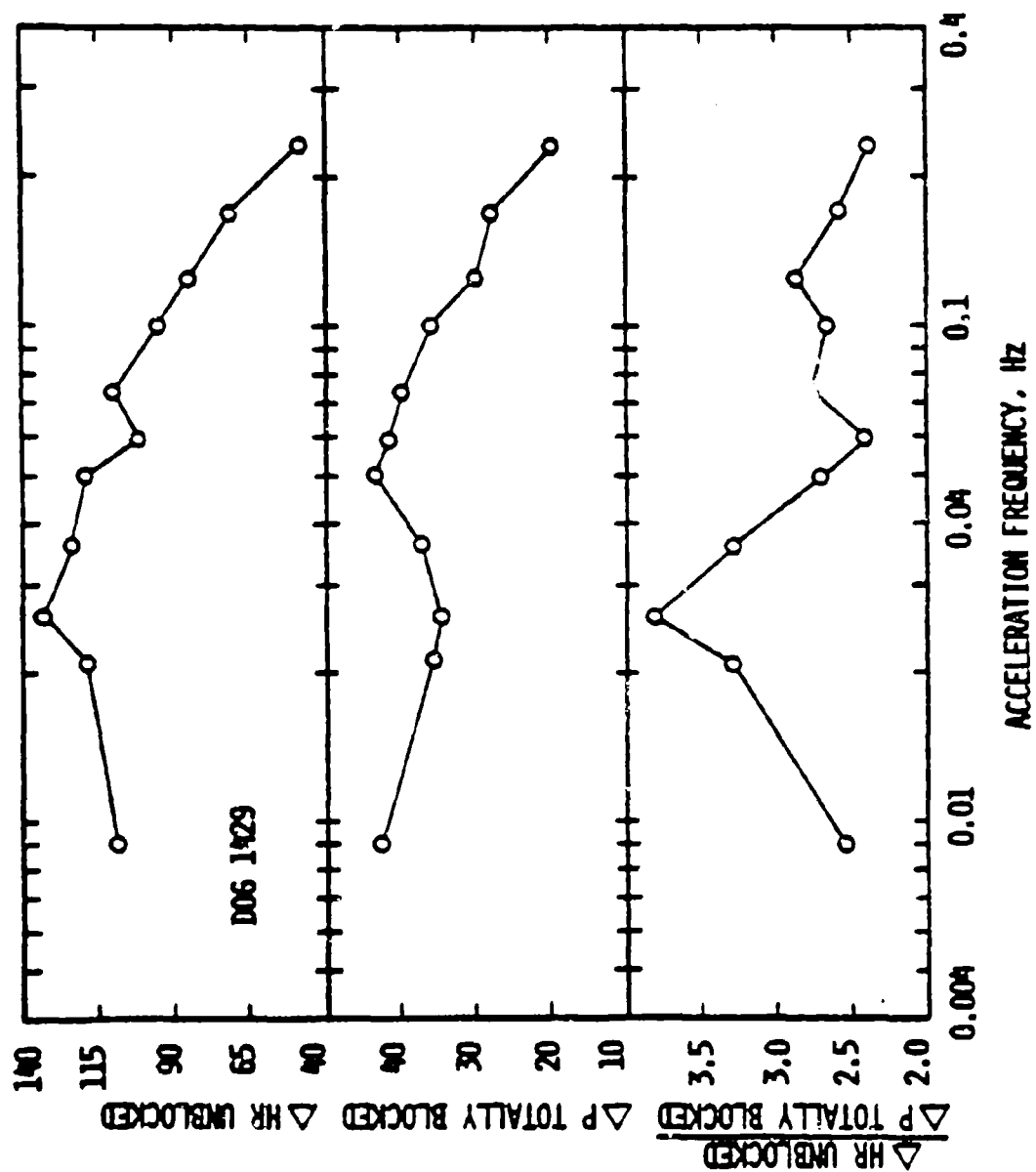


Fig. 19. Amplitude of the unblocked heart rate and blocked mean aortic pressure oscillations ( $\Delta HR$ , and  $\Delta P$ ) and  $\Delta HR/\Delta P$  versus acceleration frequency.

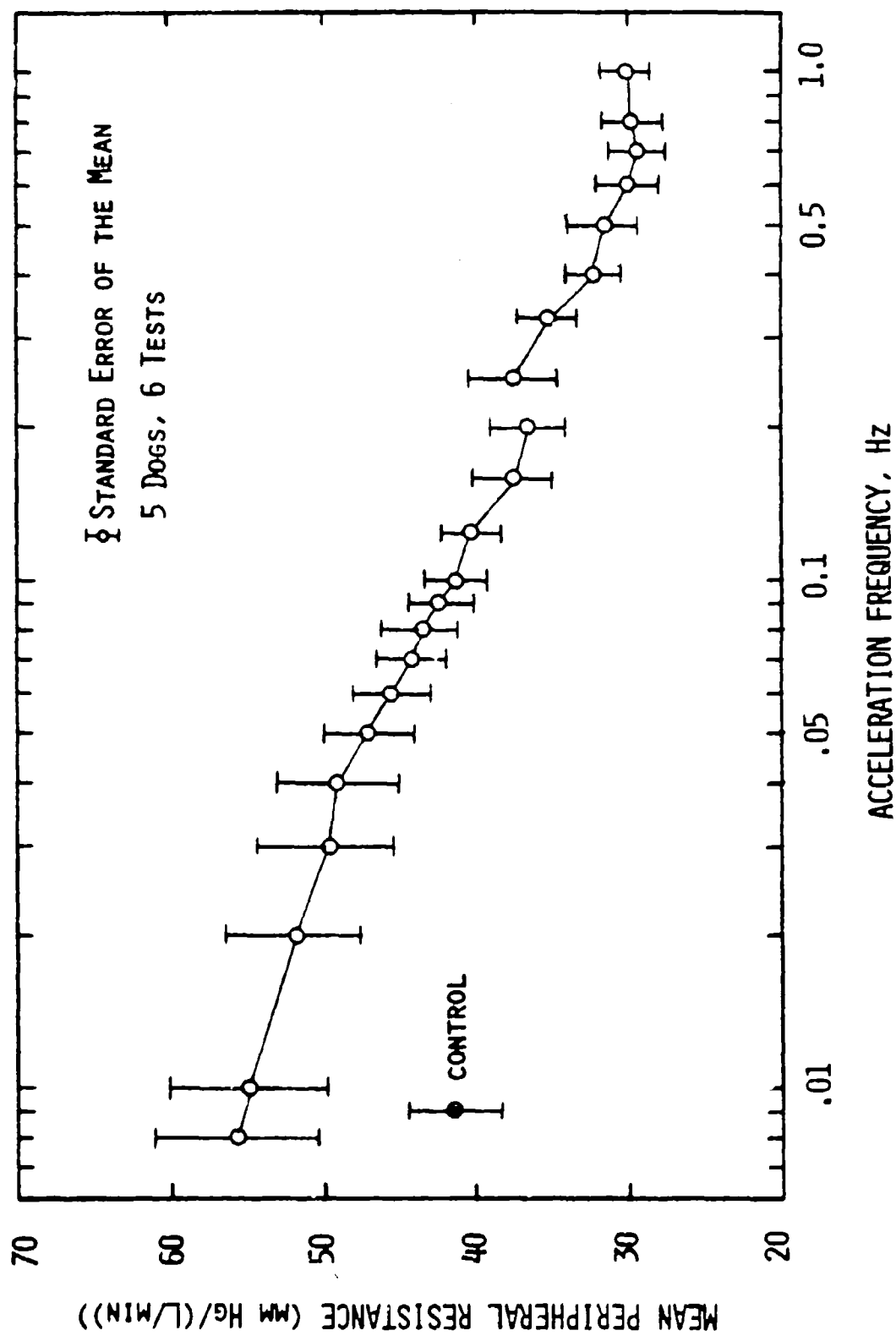


Fig. 20. Mean peripheral resistance versus acceleration frequency.

## DISCUSSION AND CONCLUSION

### Step Input Acceleration

The  $+2g_z$  steps routinely produced an instantaneous step increase in heart rate followed by a slower rise in rate and a drop in all pressures and stroke volume, followed by a slower rise in the same variables accompanied by a rise in max dp/dt. Following the peak in all variables, an increase in peripheral resistance was noted such that the return toward steady state conditions appeared to be a function of the interaction between heart rate, max dp/dt (as an indicator of inotropic activation) and peripheral resistance. The commonality of this sequence of events between subjects, leads us to propose a tentative time scale (following initiation of acceleration loadings) characterizing the cardiovascular response to  $+2g_z$  step input stress ( $> 1g/sec$ ):

Time	Event	Possible Cardiovascular Effector
1 sec	Step increase in heart rate	Withdrawal of the tonic parasympathetic signal to the sino-atrial node, unmasking the level of underlying $\beta$ sympathetic tone
1-2 sec	Drop in all diastolic pressures and peripheral resistance	probably passive (hydraulic)
2-3 sec	Slower rise in heart rate	Increased $\beta$ sympathetic signal to the SA node.
4-10 sec	Slower rise in max dp/dt (and all systolic pressures)	Increased $\beta$ sympathetic signal to myocardium resulting in an increased inotropic state.
10-30 sec	Decrease in heart rate and max dp/dt Increase in diastolic aortic pressure and peripheral resistance	Increased $\alpha$ sympathetic signal to peripheral blood vessels resulting in peripheral constriction to increase pressure
30-60 sec	Steady state operating around +stroke volume +heart rate, +peripheral resistance, and dp/dt	An interplay between increased peripheral and cardiac mechanisms in response to decreased return of blood to the heart

Perhaps the most uniform response to any of the step inputs was the response to  $-2g_z$ . In each animal, this input resulted in an instantaneous increase in all pressures, a transient increase in heart rate (with little change in stroke volume, resulting in an increase in aortic flow) and a transient decrease in peripheral resistance. Following this short lived ( $\sim 10$  sec) response, a new steady state was established, characterized by a strong sinus rhythm about the control frequency. The transient increase in heart rate, in spite of increased aortic pressure, implicates a site other than the carotid or aortic arch baroreceptors as a source for the signal.

Due to the nature of the input ( $-2g_z$  produces pressure increases on the arterial side, at the carotid and aortic arch baroreceptors, and on the venous side at the right atrium), a conflicting heart rate stimulus should occur. The increased arterial pressures should stimulate a decrease in heart rate, while the increased right atrial pressure should stimulate an increased heart rate. In Figure 5 the transient increase in heart rate (in conjunction with respiration) appears to lower right atrial pressure, but increase aortic pressure to a level sufficient to stimulate a decrease in heart rate. Then during the period of lowered heart rate the atrial pressure rises to a sufficient level to again stimulate an increase in heart rate. This sequence is repeated throughout the  $-2g_z$  test. Furthermore, the symmetry of the signal implies parasympathetic control being imposed over a constant sympathetic output.

#### Sinusoidal Acceleration

The largest amplitude of the oscillatory heart rate and mean aortic pressure responses occurred between acceleration frequencies of 0.01 and 0.1 Hz. The amplitude of these oscillatory responses then decreased sharply between 0.1 and 1.0 Hz. The wave forms of the heart rate oscillations were asymmetrical because of the difference between the time constants of the sympathetic and para-

sympathetic control of the heart. Segments of the heart rate oscillation waveforms as well as those from the step inputs observed in this study were very similar to those produced by Warner and Cox<sup>6</sup> who performed experiments in which they independently stimulated the sympathetic and vagus efferent nerves to the heart. From a comparison of their results with those of the present study, the following interpretation can be made. As a result of lowering arterial blood pressure, due to a  $+2g_z$  acceleration force, the heart rate rise was due to sympathetic stimulation coupled with parasympathetic withdrawal. This combination of efferent activity can produce the fastest increase in heart rate possible for the intact system. Yet, even for an input frequency of 0.025 Hz (Figure 7), the increase in heart rate lagged the acceleration input; and since for this frequency mean aortic pressure was in phase with the acceleration loading, the heart rate rise also lagged the decreasing mean aortic pressure. However, for the  $-2g_z$  portion of the acceleration loading (blood motion induced toward the head), the heart rate had already dropped to its lowest value within one or two beats, well in advance of the maximum acceleration loading and corresponding mean aortic pressure rise. This rapid decrease in heart rate can only be attributed to the overriding influence of parasympathetic stimulation even in the presence of high sympathetic activity. The high frequency response of the parasympathetic activity is primarily responsible for the ability of the heart rate to follow the acceleration input to frequencies up to at least 0.3 Hz for all animals tested and in some cases up to 0.7 or 0.8 Hz. The decrease in the amplitude of the heart rate oscillations after 0.1 Hz is due partly to a decrease in the amplitude of the pressure disturbances at the carotid sinus and elsewhere, and partly from the inability of the sympathetic and parasympathetic activity of the heart to follow the oscillating pressure disturbances. The hydraulic characteristics of the circulatory system appear to be responsible for the decrease in the amplitude of

the pressure disturbances for input frequencies greater than .1 Hz as demonstrated by the results from the totally blocked (hydraulic) animal preparation (Figure 18). However, it was also observed that the amplitude of the heart rate waveform from the unblocked animal decreased more rapidly than did that from the "hydraulic" animal. Thus, based on these very preliminary results, it appears that the "cut off" frequency for the intact cardiovascular system may be considerably less than .1 Hz; possibly as low as 0.03 Hz.

It is also interesting to note the difference between the amplitude of the mean aortic pressure oscillations of the normal and totally blocked animal preparation (bottom half of Figure 18). The solid line represents the pressure disturbances resulting from the hydraulic aspects of the circulatory system in response to constant acceleration loadings at various frequencies. For frequencies up to 0.03 Hz it may be reasonable to assume that peripheral vascular mechanisms aid the cardiac mechanisms and are successful in minimizing the pressure disturbances. In the acceleration frequency range from 0.035 to 0.07 Hz, the amplitude of the mean aortic pressures disturbance is considerably higher than it would be if no cardiac mechanisms were available; a maximum in the same region where the heart rate oscillations are also maximum. For acceleration frequencies greater than 0.1 Hz, the amplitudes of the mean aortic pressure oscillations are quantitatively similar to those of the totally blocked dog, possibly implying that the responses are void of any major adjustments initiated by efferent activities.

Taken collectively, the results of fourteen experiments using eight unblocked animals and two preliminary experiments using two dogs in the unblocked and blocked states, indicate that time dependent acceleration profiles whose fundamental component is between 0.01 and 0.1 Hz can be expected to produce the largest changes in heart rate and mean aortic pressure. This is not to suggest that this frequency range is necessarily hazardous, but does cer-

tainly indicate the need for continued exploration of the responses associated with sinusoidal acceleration loadings whose fundamental components are in this frequency range.

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20. to 0.3 Hz. The peak to peak amplitude of the heart rate oscillations increased with increasing frequency between 0.005 and 0.1 Hz, reaching a maximum in the range of .02 to 0.1 Hz, and then decreased rapidly, with minimal oscillations observed after 0.3 Hz. Peak to peak oscillations in aortic pressure were similar to those observed for the heart rate, with maximal oscillations in the 0.03 to 0.06 Hz range. Preliminary results using pharmacologic blockage indicate that the open loop response of aortic pressure is maximal between 0.04 and 0.06 Hz and that the influence of peripheral mechanisms is evident up to 0.03 Hz.

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